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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,292	07/05/2005	Susumu Muto	P26318	5595

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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
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Office Action Summary	Application No.	Applicant(s)	
	10/516,292	MUTO ET AL.	
	Examiner	Art Unit	
	Charleswort Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 12-31* is/are pending in the application.

4a) Of the above claim(s) *12-17, 25-27, and 30-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,18-24,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/06;3/7/0[redacted]*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response with traverse to the election requirement, mailed 4/20/07, electing compound 4 as the compound species and lung cancer as the tumor species, is acknowledged and made of record.

Applicant's statement that claims 1, 18-24, and 28-29 read on the elected species is acknowledged and made of record.

Status of the Claims

Claims 1, 12-31 are currently pending in this application.

Claims 13-16, 18-23, 24-27, 30-31 are withdrawn for examination purposes for being directed to non-elected subject matter.

Claims 1, 18-24, and 28-29 are presented for examination.

Claim of Priority

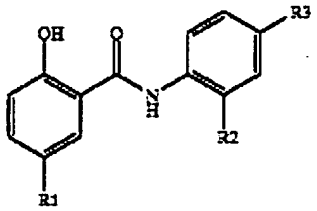
Receipt of a non-English certified copy of the foreign priority application to the instant application, received 12/8/04, is acknowledged and made of record.

Species Election

Applicant contends that the election requirement is improper, in accordance with PCT Rules 13.1 and 13.2, and should be withdrawn as the examiner failed to discuss the disclosed species in view of the prior art.

In response, applicant's traversal argument is not found to be persuasive for the reasons made of record in the Office action, mailed 4/20/07 at pages 2-4, and further in view of Callahan et al. (US patent 6,492,425).

Callahan et al. teach a method of treatment of diseases associated with NF-κB activation comprising administering to an animal, most particularly a human in need thereof, a compound of the below formula 1:



II

wherein R_A of Formula I occurs once and is R_1; and R_B of Formula I occurs twice and is independently R_2 and R_3. More specifically:

R_1 is selected from the group consisting of: H, NO_2, CF_3, F, Cl, Br, and I;

R_2 is selected from the group consisting of: H and F; and

R_3 is selected from the group consisting of: F, Cl, Br, I, phenyl and $C(O)C_{1-6}$alkyl, preferably C_{1-6}alkyl is CH_3;

and pharmaceutically acceptable salts, hydrates and solvates thereof.

Compounds of Formula II selected from the following group are most preferred for use in the methods of the present invention:

N-(4-phenyl-phenyl)-2-hydroxy-5-trifluoromethylcarboxamide;

N-(2,4-Difluorophenyl)-2-hydroxy-5-nitrocarboxamide;

N-(2,4-Difluorophenyl)-2-hydroxy-5-iodocarboxamide, and

N-(4-acetylphenyl)-2-hydroxy-5-iodocarboxamide.

wherein said diseases associated with NF-κB activation include restenosis, **cancer**, ataxia telangiestasia, AIDS, asthma (see especially abstract; and col. 3, line 17 to col 4, line 11) .

For the above reasons, the species encompassed by the instant invention are deemed to lack unity of invention as no common special technical feature exist among

the various species. Thus, the election requirement is maintained as the species are considered to lack unity of invention pursuant to PCT Rule 13.1/13.2.

Objection to the Claims

Claim 19 is objected to for reciting capitalized terms which do not confirm with proper claim language. Specifically, claim 19 recites the term "Substitutent Group."

Correction of this deficiency is requested.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 18-24, and 28-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term "and/or" The term "and" has a different meaning from the term "or." To the extent these terms are mutually exclusive, the term "and/or" render the claim unclear.

Dependent claims 18-24 and 28-29 are rejected for the same reason as these claims fail to correct the deficiency of the claims from which they depend.

Claim 19 recites the term *"wherein R^z represents hydrogen atom or a group selected from Substituent Group γ-2z; wherein Substituent Group δ-4e represents a 3,5-bis(trifluoromethyl)phenyl group, a 3-fluoro-5-(trifluoromethyl)phenyl group, a 3-bromo-5-(trifluoromethyl)phenyl group, a 3-methoxy-5-(trifluoromethyl)phenyl group, a 3-methoxycarbonyl-5-(trifluoromethyl)phenyl group, and a 3-carboxy-5-*

(trifluoromethyl)phenyl group; wherein Substituent Group y-2z represents a halogen atom, a nitro group, a cyano group, ..." The term *"wherein R^z represents hydrogen atom or a group selected from Substituent Group y-2z"* renders the claimed subject matter unclear because although the term "*a group selected from Substituent Group y-2z" implies at least two members, "Substituent Group y-2z" is the only recited member of the group.*

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 18-24, and 28-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for methods for activating PPARγ/treatment of artheriosclerosis by administering to a subject in need thereof of an effective amount of certain compounds, does not reasonably provide enablement for any and all compounds having the general formula recited in instant claim 21 or for the prophylactic/curative treatment of any and all cancers. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to a method for prophylactic and/or therapeutic treatment of tumor in a mammal including a human, which comprises the step of administering a prophylactically and/or therapeutically effective amount of a compound of general formula I as recited in claim 1.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the chemical and clinical oncological arts are generally unpredictable, requiring each embodiment to be individually assessed for chemical, pharmacologic, pharmaceutical, and clinical efficacy. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)).

Yamamoto et al. disclose that the potential applications of inhibition of the NF-κB pathway in cancer chemotherapy offer the promise of enhancing the efficacy of cancer chemotherapy and reducing abnormal cytokine production, which may contribute to the growth of certain tumors, even though such applications are in their early stages (Yamamoto et al. Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. The Journal of Clinical Investigation. January, 2001; 107(2):135-142; see especially page 141, last para; **already made of record by applicant**).

Sullivan et al. teach that AP-1 and NF-κB transcription factors regulate the expression of several critical proinflammatory proteins and cytokines and represent

attractive targets for drug discovery (Sullivan et al. 2-Chloro-4-(trifluoromethyl)pyrimidine-5-N-(3',5'-bis (trifluoromethyl) phenyl)-carboxamide: a potent inhibitor of NF-κB and AP-1-mediated gene expression identified using solution-phase combinatorial chemistry. J. Med. Chem. 1998;41:413-419; especially abstract; **already made of record by applicant**).

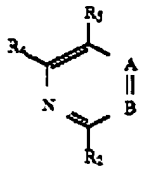
Ondrey et al. teach human head and neck squamous cell carcinomas (HNSCCs) express the propinflammatory and pro-angiogenic cytokines interleukin (IL)-1 alpha, IL-6, Il-8, and granulocyte-macrophage colony-stimulating factor in vitro and in vivo (Ondrey et al. Constitutive activation of transcription factors NF-(kappa)MB, AP-1, and NF-IL6 in human head and neck squamous cell carcinoma cell lines that express pro-inflammatory and pro-angiogenic cytokines. Mol Carcinog. Oct, 1999; 26(2):119-29, abstract only).

Mukhopadhyay et al. teach that non-small cell lung carcinoma (NSCLC) tissues expressed 2 to 20 fold-higher levels of p50 subunit of the NF-kappa B transcription factor complex than normal lung tissue in their study (Mukhopadhyay et al. Altered expression of the p50 subunit of the NF-kappa B transcription factor complex in non-small cell lung carcinoma. Oncogene. 1995; 11(5):999-1003, abstract only).

Callahan et al. teach methods of treatment of a variety of diseases associated with NF-κB activation including inflammatory disorders (e.g. rheumatoid arthritis, inflammatory bowel disease, and asthma), dermatosis (e.g. psoriasis), autoimmune diseases, tissue and organ rejection, Alzhemier's disease, stroke, atherosclerosis,

restenois, cancer (e.g. Hodgkin's disease), certain viral infections (e.g. AIDS), osteoporosis, and ataxia telangiestasia (abstract).

Suto et al. (US Patent 5,811,428) teach methods for preventing and/or treating inflammatory conditions by administering to a warm-blooded animal an effective amount of a compound of the below formula I that inhibit the kinase(s) that regulate the activation of transcription factors (TFs), such as NFκB and /or AP-1 (col. 1, line 48 to col. 11, line 46):



(I)

wherein A is C—R_6 when B is N, and A is N when B is C—R_1, and wherein R_1, R_2, R_4, R_5 and R_6 are as defined below. Thus, when A is C—R_5 and B is N, structure (I) is a pyrimidine-containing compound having structure (II), and when A is N and B is C—R_1, structure (I) is a pyrazine-containing compound having structure (III):

2. The breadth of the claims

The instant claims are relatively broad in scope. For example, claim 1 recites the term *"[a] method for prophylactic and/or therapeutic treatment of tumor in a mammal"* is very broad and encompasses, for example, the prevention/treatment of any and all tumors in any and all mammalian species. Claim 1 also recites the term *"therapeutically effective amount of a substance ... represented by ... formula (I) and a pharmacologically acceptable salt" thereof, and a hydrate thereof and a solvate thereof ..."* which is also very broad. Further, the term *"prophylactic"* given its broadest reasonable possible interpretation is construed to mean the absolute absence of any

and all evidence of tumor, which is the functional equivalent of a cure; however, cures for cancer, including pancreatic cancer, is still unknown. Because the therapeutic response to be achieved would necessarily vary depending upon the specific tumor, which would reasonably vary with the specific chemical compound species of formula I, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification discloses 268 specific compounds of the general formula I (63-99). Applicant discloses that generally the dose of the compound may be 0.01 to 5,0000 mg per day, and when used as an injection may be given 0.001 to 100 mg per day for an adult when used as an injection (page 105, first full para). Also, applicant discloses in vitro and mouse study data (Examples 1-6, pages 193-196), wherein the IC IC50 (μM) for various compounds against certain cancer cell lines is disclosed; namely, Jurkat, MIA Paca-2, HepG2, B16 melanoma, HT-1080 fibrosarcoma, NB-1 neuroblastoma, HMC-1-8 breast cancer cells (see pages 193-196, including Examples 1-6). In particular, Example 6 exemplifies an inhibitory test against cancer cell proliferation of HepG2 (human liver cancer), A549 (human lung cancer), MIA PACA-2 (human pancreatic cancer) wherein the 50% inhibitory concentration IC50 (μM), for example, for Compound 4 (i.e. HepG2 = 0.72; A549 4.03; MIA PaCa-2 0.82), versus, for example, Compound 192 (i.e. HepG2 = 11.02; A549 =23.91; MIA PaCa-2 9.42) are provided (see page 195). Based on the instant disclosure, the applicant at best has provided specific direction or guidance only for a general method of treating/preventing

tumors. No reasonably specific guidance is provided concerning useful therapeutic protocols (e.g. dosages) or specific agents for preventing all lung cancers. Further, extrapolation of the exemplified in vitro data and in vivo data disclosed by applicant to a human model would reasonably require extensive experimentation to establish a correlation between the structure-activity data and the multiple contemplated treatment effects to be achieved in practicing the instant claimed invention.

4. The quantity of experimentation necessary

In view of the uncertainty and unpredictability of the art as evidenced by the discussion of the prior art, it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention commensurate with the scope of the claims.

For the reasons stated above, claims 1, 18-24, and 28-29 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 1, and 28-29 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 1, and 28-29 are directed to encompass undisclosed *"hydrate thereof and a solvate thereof"* compounds which only correspond in some undefined way to specifically instantly disclosed chemicals. None of the undisclosed compounds meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to

> recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the disclosed chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Nonstatutory Obviousness-Type Double-Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

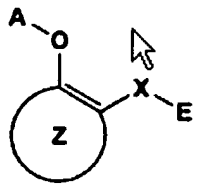
1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 18-24, and 28-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending U.S. Patent Application No. 10/564407 (appl. '407), in view of Mukhopadhyay et al. (Mukhopadhyay et al. Altered expression of the p50 subunit of the NF-kappa B transcription factor complex in non-small cell lung carcinoma. Oncogene. 1995; 11(5):999-1003, abstract only). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims as the instant claims recite the step of administering a prophylactically and/or therapeutically effective amount of a substance ... general formula (I) as the only active method step.

In particular, claim 1 of copending appl. '407 is directed towards a medicament for preventive and/or therapeutic treatment of dermal pigmentation and/or development of skin cancer, which comprises as an active ingredient a substance selected from the group consisting of a compound represented by the below general formula (I):



(I)

wherein X represents a connecting group whose number of atoms in a main chain is 2 to 5 (said connecting group may be substituted), A represents hydrogen atom or acetyl group, E represents an aryl group which may be substituted or a heteroaryl group which may be substituted, ring Z represents an arene which may have one or more substituents in addition to the group represented by formula -- O-A wherein A has the same meaning as that defined above and the group represented by formula --X--E wherein each of X and E has the same meaning as that defined above, or a heteroarene which may have one or more substituents in addition to the group represented by formula --O--A wherein A has the same meaning as that defined above and the group represented by formula --X--E wherein each of X and E has the same meaning as that defined above.

Mukhopadhyay et al. teach that non-small cell lung carcinoma (NSCLC) tissues expressed 2 to 20 fold-higher levels of p50 subunit of the NF-kappa B transcription factor complex than normal lung tissue in their study (abstract).

Thus, claims 1, 18-24, and 28-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the copending appl. claims 1-16.

For the same reasons stated above, claims 1, 18-24, and 28-29 are similarly deemed to be obvious variants of the limitations of the subject matter of claims 1-3 of copending US Patent Application No. 10/577,487.

These are provisional obviousness-type double patenting rejections because the conflicting claims of the copending applications have not in fact been patented.

Claim rejections – 35 USC 103(a)

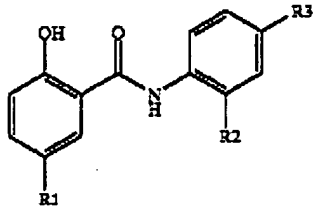
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 18-24, and 28-29 are rejected under 103(a) as being unpatentable over Callahan et al. (US Patent 6,492,425), in view of Mukhopadhyay et al. (Mukhopadhyay et al. Altered expression of the p50 subunit of the NF-kappa B transcription factor complex in non-small cell lung carcinoma. Oncogene. 1995; 11(5):999-1003, abstract only).

Callahan et al. teach methods of treatment of a variety of diseases associated with NF-κB activation including inflammatory disorders (e.g. rheumatoid arthritis, inflammatory bowel disease, and asthma), dermatosis (e.g. psoriasis), autoimmune diseases, tissue and organ rejection, Alzhemier's disease, stroke, atherosclerosis, restenois, cancer (e.g. Hodgkin's disease), certain viral infections (e.g. AIDS), osteoporosis, and ataxia telangiestasia (see abstract, and col. 3, line 17 to col. 4, line 54).



wherein R_A of Formula I occurs once and is R_1; and R_B of Formula I occurs twice and is independently R_2 and R_3. More specifically:

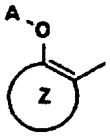
R_1 is selected from the group consisting of: H, NO_2, CF_3, F, Cl, Br, and I;

R_2 is selected from the group consisting of: H and F; and

R_3 is selected from the group consisting of: F, Cl, Br, I, phenyl and $C(O)C_{1-6}$alkyl, preferably C_{1-6}alkyl is CH_3;

The term *"[a] method for prophylactic and/or therapeutic treatment"* as recited in instant claim 1 is construed to encompass conditions other than tumors as the term

"prophylactic" given its broadest reasonable possible interpretation is construed to mean the absolute absence of tumor. Claim 1 recites the term *"tumour" which is the functional equivalent of the term "cancer."* The claimed general formula as recited in claim 1 represents the same general core structure taught by Callahan et al. as having the same therapeutic use i.e. treating conditions associated with NF-κB activation. Callanhan et al. also teach methods of treating conditions associated with activation of NF-κB activation (see abstract). However, Callahan et al. do not exemplify the instant claimed 3,5-bis(trifluoromethyl)phenyl substitutent equivalent to "E" substitutent recited in instant claim 1. Based on the prior art, it is within the skill and knowledge of an artisan skilled in the art to modify the core structure taught by Callahan et al. to create the instant claimed 3,5-bis(trifluoromethyl)pheny compounds, including the elected compound 4, wherein:



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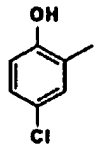
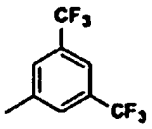


and E=



Mukhopadhyay et al. teach that non-small cell lung carcinoma (NSCLC) tissues expressed 2 to 20 fold-higher levels of p50 subunit of the NF-kappa B transcription factor complex than normal lung tissue in their study (abstract).

Based on the teaching of Mukhopadhyay et al., someone of skill in the art would have been motivated to create the instant claimed inventive concept.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability in view of the above cited prior art.

Relevant Art of Record

The below cited art references made of record and relied upon are considered pertinent to applicant's invention.

Yamamoto et al. disclose that the potential applications of inhibition of the NF-κB pathway in cancer chemotherapy offer the promise of enhancing the efficacy of cancer chemotherapy and reducing abnormal cytokine production, which may contribute to the growth of certain tumors, even though such applications are in their early stages (Yamamoto et al. Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. The Journal of Clinical Investigation. January, 2001; 107(2):135-142; see especially page 141, last para; **already made of record by applicant**).

Sullivan et al. teach that AP-1 and NF-κB transcription factors regulate the expression of several critical proinflammatory proteins and cytokines and represent attractive targets for drug discovery (Sullivan et al. 2-Chloro-4-(trifluoromethyl)pyrimidine-5-N-(3',5'-bis (trifluoromethyl) phenyl)-carboxamide: a potent inhibitor of NF-κB and AP-1-mediated gene expression identified using solution-phase combinatorial chemistry. J. Med. Chem. 1998;41:413-419; especially abstract; **already made of record by applicant**).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

3 December 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER